TOXIC EFFECTS OF SALVARSAN.*

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Without decrying the use of salvarsan in cases where it is properly indicated and where experience has shown it to be a most potent remedy, it is desired in this paper to call attention to some of the accidents following its use which have appeared in the literature, and to discuss those cases of arsenic intoxication resulting from it in whom there was no evident contra-indication.

Synthetic arsenic compounds have been in use for some time,—as sodium cacodylate, atoxly, arsacetin. Sodium cacodylate is a sodium salt of cacodylic or dimethyl-arsenic acid, which differs from arsenic acid by replacement of two hydroxyl groups by two methyl groups. Thus:

$O\ As.\ (OH)_3$ — Arsenic Acid.

$O\ As.\ (CH_3)_2\ OH$ — Cacodylic Acid.

$O\ As.\ (CH_3)_2\ ONa$ — Sodium Cacodylate.

Atoxyl is sodium arsanilate. Arsanilic acid differs from arsenic acid in that one hydroxyl group of the arsenic acid is replaced by an amino-benzene. Thus:

$O\ As.\ (OH)_3$ — Arsenic Acid.

$O\ As.\ (C_6\ H_4\ NH_2)\ (OH)_2$ — Arsanilic Acid.

$O\ As.\ (C_6\ H_4\ NH_2)\ (OH)\ ONa$ — Atoxyl.

It is a relatively stable salt of arsenic acid quite soluble in water and practically neutral in reaction. Arsacetin or sodium acetyl arsanilate is the sodium salt of acetyl arsanilic acid, which differs from arsanilic acid in that one hydrogen atom of the amino group is replaced by an acetic acid residue. Thus:

$O\ As.\ (C_6\ H_4\ NH_2)\ (OH)_2$
Arsanilic Acid.

$O\ As.\ (C_6\ H_4\ NH.\ CH_3\ CO)\ (OH)_2$.
Acetyl Arsanilic Acid.

$O\ As.\ (C_6\ H_4\ NH.\ CH_3\ CO)\ (OH)\ (ONa)$
Arsacetin.

The Ehrlich-Hata preparation which we know as salvarsan is distantly related to sodium cacodylate, atoxyl and arsacetin. Its structural formula is

$NH_2.\ OH.\ C_6\ H_3.\ As: As.\ C_6\ H_3.\ OH.\ NH_2$

which chemical constitution may be indicated by the name diamino-dihydroxy-arseno-benzene.

The arsenic content of salvarsan is 35.16%, so that in the average dose of 0.6 gm. of salvarsan the patient receives about 1½ grains of metallic arsenic. Neosalvarsan is similar in action to salvarsan, having the advantage of solubility in water and freedom from the danger of acidity. The arsenic content in three parts is equal to two of salvarsan, so that the average dose is larger, being for men 0.75 gm. Elimination of arsenic after intravenous injection of salvarsan is slow. In Alt's clinic where salvarsan was first used by Dr. Hoppe it was found that arsenic was eliminated in the urine slowly and found as late as the 11th day,—0.3 of a gram had been given. Bornstein [1] found upon examination of some cadavers who two weeks to several months before death had been subjected to injections of salvarsan, that the arsenic was stored up in the liver, kidneys and spleen.

Certain organic diseases are an absolute contra-indication to the use of salvarsan, while the presence of others require its use with caution. According to Ehrlich, the triad, aortitis, coronary sclerosis and myocarditis should absolutely contra-indicate the use of the drug. The elaboration of that rule demands the exercise of caution where there is disease of the blood vessels, all myocardial diseases of the heart or nephritis either acute or chronic. Advanced diseases of the cerebro-spinal system, as tabes dorsalis, where considerable damage has already been accomplished, are contra-indications, and also in those conditions where syphilitic meningitis comes into question it should be used with great care. Death has followed its use repeatedly in cerebro-spinal lesions at which the autopsy showed leptomeningitis, generalized congestion of the brain or a reaction of the syphilitic focus involving a vital center. General paresis is a contra-indication to the use of salvarsan for similar reasons. Disease of the optic or auditory nerve of central origin probably should be considered a contra-indication. J. F. Schamberg [2] collected fifteen cases of optic neuritis following salvarsan and nineteen cases of auditory nerve disturbance in something like 50,000 cases. It may be that this collection was incomplete. In addition, accidents may happen from salvarsan without appreciable cause. Mann [3] reports a salvarsan accident in a strong patient who had always been well. Three days after intravenous injection the patient became unconscious with complete loss of all recollection and sensibilities. This lasted three days and gradually subsided. Kannengiesser [4] observed in a robust butcher of 29 epileptiform convulsions three hours after injection, followed by death. Autopsy failed to show satisfactory explanation. Gaucher [5] reports a corpulent man who upon examination showed no cardiac, renal or cerebral trouble, and four days after 0.6 gms. of salvarsan the patient was found lying in his room completely unconscious and moving convulsively. The following day he was in the same stupor, convulsive crises recurred, cyanosis, perspiration, rapid pulse, a rise of temperature to 105° F.,—at autopsy a leptomeningitis. Another case was of a man of 21 who at autopsy showed generalized congestion of the brain and lungs.

The Italians experimenting in the earlier history of salvarsan found that small doses apparently caused an increase in the syphilitic process, apparently only sensitizing the patient to the action of the spirochetae.

Naturally, the thought that occurs in considering these reported cases is the question of anaphylaxis and cumulative action.

Case 1. Minnie B., housewife, age 35, was ad-

* Read before the California Academy of Medicine, July 20, 1913.

mitted to hospital six months after an initial lesion on the vulva and presented a general syphilitic eruption with mucous patches in the mouth and enlarged glands. She had had malaria, was a sufferer from epilepsy which had begun when she was fifteen years old and had continued to the present time, the attacks occurring previous to her menstrual period, and occurring sometimes three times a day. She was addicted to the use of alcohol. The heart appeared normal, the urine showed a trace of albumin, no casts were found. The patient was given 0.6 gms. of salvarsan intravenously and within a few miutes there followed an epileptiform convulsion after which the patient sank into a coma and died in three days. No autopsy. This case is possibly similar to the one described by Kannengiesser, and suggests anaphylaxis, although it has to be admitted that in the absence of an autopsy nothing definite can be said.

Case 2. John X. This patient is a man 51 years old, a wool sorter by occupation who twenty years ago contracted syphilis, with the usual secondary manifestations. Three years ago he began to have symptoms referable to multiple syphilitic sclerosis of the brain and cord, which at the time interfered with his walking to a considerable extent.

At the present time he has a marked Rhomberg, slight nystagmus, unequal pupils (old iritis), incontinence of the bladder, intractable constipation, as well as increased knee reflexes, double Babinsky, but no sensory changes and no Argyll-Robertson pupil. In short multiple motor tract lesions. The interesting point in this case is that after the last dose of salvarsan which he had two months ago, his constipation became extremely bad, while prior to that time it was only moderate. It would seem in this case that focal edema following the salvarsan injection in the cord caused damage to the already impaired center of defecation, and while this man still must be considered syphilitic, he should be placed in the class where salvarsan is contraindicated.

Case 3. Mr. D. H. D., age 34. This patient presented himself October 18, 1912, having had recurred ascites for the preceding seven months for which he had been repeatedly tapped, and for which an exploratory laporatomy had been made, when the operator found "a large malignant tumor occupying the right lobe of the liver and firmly bound to or directly involving the colon, gall bladder, duodenum and pylorus. This operation followed seven months' treatment based on a positive Wassermann." Physical examination showed when he came to me, a large, irregular liver extending about to the umbilicus and the abdomen full of ascitic fluid; examination of urine negative and Wassermann; complement fixation reaction for syphilis was strongly positive. A diagnosis of syphilitic hepatitis was made and patient started on the usual treatment of mercury and iodide. In addition he has received to the present time, July 26th, six doses of salvarsan and the fluid has been drawn from his abdomen innumerable times. The salvarsan treatment was followed by promptly beneficial results, so that after the second injection he was able to go from 22 to 24 days without paracentesis of the abdomen instead of every seven to ten days as before. His record shows that on November 23, 1912, he received 0.6 gms. of salvarsan, and neosalvarsan on December 14, 1912, January 31st, March 26th, and July 2, 1913. With the exception of the last injection no unusual ill effects were observed, but immediately upon the fifth injection he noticed a very strong taste in his mouth which he found it difficult to describe. He felt ill on the way to his home, was dizzy and nauseated,—went immediately to bed and has no recollection whatever of the events during the succeeding week. Two days afterward his family sent for me and I found him in bed in an extreme agony of nervousness. He had been vomiting for about two days, had complete anuria which lasted altogether three days, and a subnormal temperature. Physical examination showed the mucous membranes very dry and the cutaneous nerves, especially of the forehead, very sensitive and painful. Marked icterus was present. The patient was in a dazed mental condition, although he could be roused, and would talk. The lungs showed nothing. The heart was rapid and the pulse very weak. During the succeeding two or three days he expectorated some rusty sputum (although nothing was to be found upon examination of the lungs), and developed a very extensive herpes labialis. With the return of the renal function the urine showed the usual signs of a severe acute nephritis which has been during the last three weeks gradually subsiding. At the present time also he shows heavy desquamation of his hands and feet, and, to a lesser degree, of the skin of the entire body. There is formication of the skin over the trunk. He therefore had, following this neosalvarsan, a very severe arsenical poisoning. For several days it appeared that the patient would certainly die, so great was the degree of arsenic intoxication.

The lesson to be learned from this case is by no means clear. It is possible that the cases with syphilis of the liver respond in a somewhat different manner from others; it is possible that there was an error of technic, although the ability of the man to whom he was sent for salvarsan injection, in my opinion, precludes that consideration. It may be, as is most likely, that in some manner which we do not know there occurred cumulative action of salvarsan. It is to be regretted that the urine was not tested to determine the duration of the arsenic elimination after each dose, as would appear to be advisable where repeated injections of salvarsan are to be employed.

Finally, the question of anaphylaxis comes into discussion upon the ground that the preceding doses had sensitized the patient, and this hypothesis may be borne out by the case of Kannengiesser already mentioned.

REFERENCES.

1 Deutsche med. Woch., Jan. 19, 1911.
2 Jr. A. M. A., May 20, 1911.
3 Muenchen med. Woch., Vol. 58, No. 30, p. 1672.
4 Muenchen med. Woch., Vol. 58, No. 34, p. 1806.
5 Jr. A. M. A., Vol. 57, No. 25, p. 2007.

Discussion.

Dr. L. S. Schmitt—The reactions of patients to salvarsan should be divided into two classes: one, the very definite arsenical poisoning, and the other the so-called Huxeheimer reactions, whether on the skin or in the internal organs.

Dr. Schmitt—It seems that patients with liver and central nerve involvement undoubtedly react stronger to salvarsan than other classes of luetics. This is manifested mainly by a flare up of the lesions. The hepatitis we have in lues is accompanied by a marked increase of interstitial tissue. There is a sudden breaking down of this interstitial tissue, and the bringing of salvarsan into close contact with the foci of spirochaetes would undoubtedly cause some of the reaction in this particular instance.

As to the unconsciousness, we know definitely that leptomeningitis is common, and when mercury has been given with salvarsan and immediately following it, the percentage of cases of unconsciousness, severe headaches, or other conditions referable to the central nervous system, are markedly less. I recall an instance of a man who had an infection forty-one years prior to the appearance of the hepatitis. The first dose of salvarsan brought on a rather severe reaction, so much so that we were afraid of the outcome. We used salvarsan the second time, following it with

mercury intravenously, without any reaction. We can infer from this and other evidence that we have a definite reaction from the luetic source as well as from the arsenical condition.

As to the question of anaphylaxis, I believe the use of that word in connection with the drug is erroneous.

We ordinarily have a marked complement fixation reaction in lues where the liver is involved, probably due to the fact that there is a marked increase of lipoid substances in the liver; therefore we undoubtedly get very marked reactions in such leutics as these. This man will undoubtedly have a complement fixation reaction for some time to come and this should be considered from two standpoints: one—whether it measures the virulence of the infection; the other—does it measure his reaction to the infection? If the latter is true, a marked reaction should not alarm us at all in this class of cases. However, the so-called Wassermannfast individuals have a greater chance of recurrence than those in whom the reaction eventually becomes negative.

Major Roger Brooke—I have seen several unfortunate results following the administration of salvarsan. I remember late in 1910, or early in 1911, when we first received salvarsan in the Philippines, many patients applied for treatment that had no active manifestations at the time. There was one man who was given a dose intramuscularly and sent to the ward. He appeared all right and after lying down a little while got up and ate lunch. At 2:30 the ward man reported the patient unconscious, and I went to look at him. He had stertorous respiration, could not be aroused, and that condition kept up for three days or until the end. The man could apparently hear, but could not talk or move his arms or legs. He could, however, move his eyelids. He apparently understood questions and would indicate yes or no by opening or closing his eyelids. About eight hours before the end he developed a retraction of the head and at autopsy we found meningitis with a moderate amount of exudation. As far as we could find there was no evidence of meningitis beforehand.

A year ago I saw two other cases which shortly after the administration of salvarsan developed symptoms that simulated quite closely the hebephrenic form of dementia praecox, but they followed within twenty-four hours of the injection of salvarsan and cleared up within three or four weeks.

Dr. Harry E. Alderson—I would like to ask Dr. Ebright if he said that the last patient had desquamation of the skin elsewhere than on the palms and soles. (Dr. Ebright replied affirmatively.) The desquamation on the palms and soles is rather fine in character and, taken in connection with the generalized desquamation, it occurs to me that it may have been due to some other form of toxemia. One specific result of the action of arsenic on the skin is the appearance of keratoses and hyperkeratoses of the palms and soles. This man had a series of injections of salvarsan, and if the arsenic effect was so great, why did he not develop keratoses of the palms and soles and other parts instead of a generalized desquamation?

Dr. Ebright, closing discussion: Salvarsan should be withheld in cerebrospinal cases at least until other forms of treatment have been tried.

HOW TO READ THE PNEUMOTHORAX MANOMETER.

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Now that the value of induced pneumothorax in the treatment of pulmonary tuberculosis is being generally recognized, it is of considerable importance that the records of different observers should be easily understood by their readers. All workers in this field agree that the manometer is an essential part of the apparatus and that it is absolutely essential to a proper estimation of intrathoracic pressures. Under these circumstances it is somewhat surprising to note that various workers are reading and recording their manometers differently. So that at the present time one is at a loss to know what a writer means by his figures. To make my meaning clearer I will take an illustrative example.

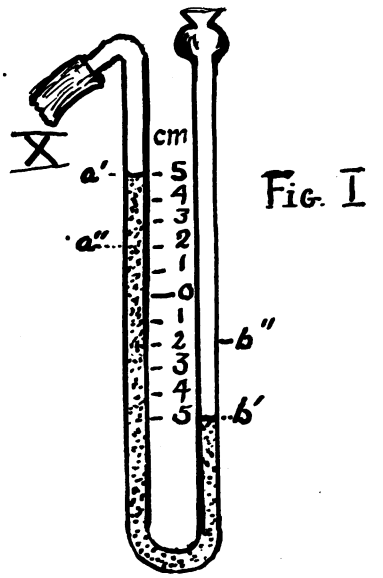

Fig. I

In Figure 1 the ordinary manometer is depicted, being simply a U glass tube, filled with water to zero. Thoracic pressures are transmitted through a tube X, and depress (positive pressure) or "suck up" (negative pressure) the fluid. If the pressure varies as during breathing, of course the columns will oscillate. For example, the left column Figure 1, under negative pressure, oscillates from a' to a", and simultaneously the right oscillates from b' to b". During breathing they are in constant motion. Now the question answered so variously is how should the manometer be read.

Should one read in this case negative pressure 5, the top figure to which the left column rises; or 2 the lowest mark above zero that it reaches; or 10, the difference between the tops of the two columns when they are at their maxima; or 4, the difference between them when they are at their minima; or should one read the mean, the figure in the middle of the space covered by the oscillations between the maximum and minimum on one side of the manometer—in this case 3.5; or, finally, should this figure be doubled making the reading 7, the MEAN PRESSURE?

Such is the confusion of possibilities that present themselves to some minds. Of course there can be but one correct reading. Physics has long ago made clear that the pressure is measured by the column of fluid supported. Now the column supported is that portion of the longer column above the top of the shorter. The correct maximum reading in the given example is, therefore, negative 10, while the correct minimum reading is negative 4.

But under these conditions some would read maxima, and some would read minima. So we still have something to agree on. It is here suggested that **MEAN PRESSURES only be recorded.** In this example the mean pressure is negative 7.